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(54) Title: PREPARATION OF 2,5-DICHLOROBENZOPHENONES (57) Abstract A method for preparing isomerically pure 2,5-dichlorobenzophenones in good to high yields is provided. The invention comprises Friedel-Crafts arylation of 1,4-dichlorobenzene using an aroyl halide or aromatic anhydride and at least one Lewis acid, the latter being present in an amount of at least about 1.1 mole per mole of aroyl halide or aromatic anhydride, preferably about 1.5 moles per mole of aroyl halide or aromatic anhydride and, more preferably, from about 2 to about 2.5 moles of Lewis acid per mole of aroyl halide or aromatic anhydride. Preferably, the molar ratio of 1,4-dichlorobenzene to aroyl halide ranges from about 1.2 : 1 to about 8 : 1.		

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PREPARATION OF 2,5-DICHLOROBENZOPHENONES

Field of the Invention

This invention relates to methods for preparing 2,5-dichlorobenzophenones, and in particular, methods employing Friedel-Crafts arylation of 1,4-dichlorobenzene.

Background of the Invention

Benzophenones are very useful in organic synthesis in general and in the pharmaceutical industry in particular. Although it is common to prepare benzophenones by Friedel-Crafts benzylation, known methods of preparing 2,5-dichlorobenzophenones from 1,4-dichlorobenzene have had very limited success and have been characterized by low conversion, low yield and difficulty in purification due to isomeric contamination of the desired 2,5-dichlorobenzophenone. Moreover, previous attempts to prepare 2,5-dichlorobenzophenones from 1,4-dichlorobenzene commonly have used nitrobenzene as a solvent. Nitrobenzene is highly toxic and its use is regulated. All of these factors limit the possibility of commercial-scale preparation of 2,5-dichlorobenzophenones from 1,4-dichlorobenzene.

In one example of the prior methods just described, after heating dichlorobenzene and benzoyl chloride with aluminum chloride for 49 hours at 150° to

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1 170°C, 2,5-dichlorobenzophenone was obtained in only
20% yield. (Th. de Crauw, *Rec. Trav. Chim. Pay Bas* 50,
767, (1931)). In another case,
2,5-dichlorobenzophenone was obtained in 0.8% yield,
5 together with appreciable amounts of other isomers,
after running the reaction in nitrobenzene for 10 hours
at 100°C (P. A. Goodman et al., *J. Chem. Soc. (C)* 2452,
(1968)). Other unsuccessful examples can be found in
the literature. See, e.g., J. Ganzmuller, *J. Prakt.*
10 *Chem.* 138, 311, (1933); P. H. Gore et al., *Zh. Org.*
Khim., 1145, (1967) 10% yield; M. Godfrey et al.,
Tetrahedron, 32, 843, (1976) (0.8% yield).

Higher yields of pure 2,5-dichlorobenzophenones
have been obtained by starting with 2,5-dichlorobenzoyl
15 chloride. (B. M. Zarnegar, Canadian Patent No.
1,153,369, granted to Mobil Oil Corporation U.S.A.).
This aroyl chloride is not commercially available and
has to be synthesized from expensive
2,5-dichlorobenzoic acid. Moreover, when
20 2,5-dichlorobenzoyl chloride reacts with substituted
benzenes, e.g., toluene, regiosteric isomers usually
cannot be avoided. Such a synthetic scheme is
unattractive.

Accordingly, a need exists for an inexpensive
25 method for preparing isomerically pure
2,5-dichlorobenzophenone and substituted analogs from
1,4-dichlorobenzene in high yield.

Summary of the Invention

30 It has now been discovered that 2,5-
dichlorobenzophenone and a broad class of substituted
analogues of 2,5-dichlorobenzophenone can be prepared in
high yield and with isomeric purity using the method of
Friedel-Crafts aroylation of 1,4-dichlorobenzene in the
35 presence of a suitably large amount of Lewis acid
catalyst. More specifically, heating a mixture of an
aroyl halide, 1,4-dichlorobenzene and at least one

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1 Lewis acid present in an amount of at least about 1.1
mole per mole of aroyl halide, preferably about 1.5
mole per mole of aroyl halide, more preferably about 2
5 to about 2.5 mole of Lewis acid per mole of aroyl
halide results in a high yield (greater than about 50%)
of isomerically pure 2,5-dichlorobenzophenones.

A variety of substituted and unsubstituted aroyl
halides can be used to produce 2,5-dichlorobenzophenone
analogues in accordance with the present invention.
10 Without limitation, these include benzenecarbonyl
halides ("benzoyl halides"), arylcarbonyl halides
("aroyl halides") and heteroarylcarbonyl halides
("heteroaroyl halides"). For convenience, all of these
reactants are referred to herein as "aroyl halides."

15 In addition to aroyl halides, other activated
forms of aromatic acids can be used in the present
invention, including, e.g., substituted and
unsubstituted anhydrides such as phthalic anhydride,
benzoic anhydride and the like.

20 The aroylation products of the method provided by
the present invention can be used as starting materials
for general, pharmaceutical and polymer synthesis.

Detailed Description of the Invention

25 This invention provides a method of preparing pure
2,5-dichlorobenzophenone and substituted analogues in
high yield from 1,4-dichlorobenzene and aroyl halides.
The isomeric purity of the 2,5-dichlorobenzophenones
produced is greater than about 99.5%.

30 The invention resides in the discovery that
Friedel-Crafts aroylation of 1,4-dichlorobenzene
proceeds in high yield and gives isomerically pure
products if a Lewis acid catalyst is present in large
amount relative to the amount of aroyl halide reactant.
35 More particularly, the invention comprises
Friedel-Crafts aroylation of 1,4-dichlorobenzene using
an aroyl halide and at least one Lewis acid catalyst

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1 preferably present in an amount of at least about 1.5
mole -- more preferably from about 2 to about 2.5 mole
-- per mole equivalent of aroyl halide.

Starting material ratios as low as 1.1/1.3/1
5 (moles of AlCl_3 : 1,4-dichlorobenzene : benzoyl
chloride) have been found sufficient to produce 2,5-
dichlorobenzophenone in about 50% yield under the
conditions provided by the present invention; the same
ratio of starting materials has been found to give a
10 64% yield of 2,5-dichlorobenzophenone if the benzoyl
chloride is added slowly to a mixture of AlCl_3 , 1,4-
dichlorobenzene and a small amount of benzoyl chloride.

Higher relative amounts of Lewis acid improve
yield and product purity and increase the speed of
15 reaction. The trade-off is the cost of additional
Lewis acid and increased amounts of by-products
requiring disposal. Lower relative amounts of Lewis
acid require a higher temperature and a longer reaction
time; this may account for some of the earlier failures
20 reported in the literature. More Lewis acid is
required in the presence of donor substituents. As
discussed below, excess 1,4-dichlorobenzene also has
been found to improve product yields.

The products of the method described herein are
25 2,5-dichlorobenzophenones, meaning 2,5-
dichlorobenzophenone and substituted analogs thereof.
Such compounds are polynuclear aromatic ketones in
which one moiety attached to the carbonyl group is a
2,5-dichlorophenyl group, and the other moiety is an
30 aryl or heteroaryl group, which may be substituted or
unsubstituted. For convenience, the term "2,5-
dichlorobenzophenones" is defined to include both 2,5-
dichlorobenzophenone and substituted analogs thereof.

The aroyl halides used to produce these compounds
35 include, without limitation, substituted and
unsubstituted: benzenecarbonyl halides ("benzoyl
halides"), arylcarbonyl halides ("aroyl halides") and

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1 heteroarylcarbonyl halides ("heteroaroyl halides").
For purposes of nomenclature, all such compounds are
referred to herein (and in the appended claims) as
"aroyl halides," unless the context indicates
5 otherwise. Structurally, the aroyl halides can be
viewed as comprising benzoyl halides or heteroaroyl
halides having from 0 to 5, or 0 to 4, non-hydrogen
substituents bound to the benzoyl or heteroaroyl ring,
respectively, each of which does not interfere with
10 Friedel-Crafts arylation. Each substituent is bound
to the benzoyl or heteroaroyl ring either directly or
through a carbon atom or a heteroatom comprising,
without limitation, sulfur, phosphorus, oxygen,
nitrogen, or silicon.

15 For example, the aroyl halide used to prepare
2,5-dichlorobenzophenone is benzoyl chloride (or other
halide: bromide, iodide, and the like), which has zero
non-hydrogen substituents; the benzoyl ring has a
hydrogen atom at all five positions. Similarly, an
20 aroyl halide (actually, a heteroaroyl halide) for
preparing 3'-pyridinecarbonyl-2,5-dichlorobenzene is
nicotinoyl halide, which has zero non-hydrogen
substituents. In contrast, 2-methoxybenzoyl chloride
has one non-hydrogen substituent: a methoxy group
25 bound to the benzoyl ring at the 2 position.
1-Naphthoyl chloride can be viewed as a benzoyl ring
having two non-hydrogen substituents (both carbon
atoms) bound to the benzoyl ring at adjacent ortho-and
metapositions on the ring, due to the fused ring
30 structure of naphthalene.

Any aroyl halide can be used as long as it does
not interfere with arylation. Thus,
p-chloromethylbenzoyl chloride is not particularly
useful because the chloromethyl group causes formation
35 of complicated reaction products. Some non-limiting
examples of useful aroyl halides are: benzoyl
chloride, 1-naphthoyl chloride, 2-naphthoyl chloride,

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1 4-quinolinoyl chloride, nicotinoyl chloride (3-pyridinecarbonyl chloride), isonicotinoyl chloride (4-pyridinecarbonyl chloride), p-toluoyl chloride, m-toluoyl chloride, o-toluoyl chloride, phthaloyl
5 chloride, isophthaloyl chloride, terephthaloyl chloride, 4,4'-biphenyldicarbonyl chloride, 2,3-dimethylbenzoyl chloride, 2,4-dimethylbenzoyl chloride, 2,5-dimethylbenzoyl chloride, 2,6-dimethylbenzoyl chloride, 3,4-dimethylbenzoyl chloride,
10 3,5-dimethylbenzoyl chloride, 2-benzoylbenzoyl chloride, 3-benzoylbenzoyl chloride, 4-benzoylbenzoyl chloride, 2-fluorobenzoyl chloride, 3-fluorobenzoyl chloride, 4-fluorobenzoyl chloride, 2-chlorobenzoyl chloride, 3-chlorobenzoyl chloride, 4-chlorobenzoyl chloride,
15 2-trifluoromethylbenzoyl chloride, 3-trifluoromethylbenzoyl chloride, 4-trifluoromethylbenzoyl chloride, 2-methoxybenzoyl chloride, 3-methoxybenzoyl chloride, 4-methoxybenzoyl chloride, 2-methoxycarbonylbenzoyl chloride, 3-methoxycarbonylbenzoyl chloride, 4-methoxycarbonylbenzoyl chloride, 2-cyanobenzoyl chloride, 3-cyanobenzoyl chloride, and 4-cyanobenzoyl chloride. Aroyl halides besides aroyl chlorides may be
20 used, including without limitation, aroyl bromides, aroyl iodides, and the like. Thus, 2,5-dichlorobenzophenone can be prepared by Friedel-Crafts aroylation of 1,4-dichlorobenzene using benzoyl bromide and at least one Lewis acid.

25 In addition to aroyl halides, other activated forms of aromatic acids can be reacted with 1,4-dichlorobenzene in the presence of one or more Lewis acids to produce substituted analogs of 2,5-dichlorobenzophenone. Non-limiting examples include
30 substituted and unsubstituted aromatic anhydrides (both of which are referred to herein as aromatic anhydrides), such as phthalic anhydride, benzoic
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1 anhydride, substituted phthalic anhydrides and
substituted benzoic anhydrides. The substituents (non-
hydrogen atoms) on "substituted" aromatic anhydrides
are limited to functional groups that do not interfere
5 with Friedel-Crafts aroylation of 1,4-dichlorobenzene.
In general, 2,5-dichlorobenzophenones prepared in
accordance with the present invention can be made using
an acid halide or its corresponding anhydride,
including the anhydride analogs of the acid chlorides
10 listed above. The preferred and other ratios of
reactants described herein (e.g., Lewis acid-to-aroyl
halide, 1,4-dichlorobenzene-to-aroyl halide) apply
equally to reactions in which an aromatic anhydride is
used in place of an aroyl halide.

15 Although not bound by theory, in view of past
failures to prepare isomerically pure 2,5-
dichlorobenzophenones in substantial yield using
Friedel-Crafts aroylation of 1,4-dichlorobenzene in the
presence of only small amounts of Lewis acids, it is
20 believed that the present invention's success is owed
to the relatively large Lewis acid-to-aroyl halide
ratio used in the Friedel-Crafts aroylation of 1,4-
dichlorobenzene. In particular, it is believed that
side reactions are somehow suppressed, or, perhaps more
25 correctly, the reaction of an aroyl halide or other
activated aromatic acid with 1,4-dichlorobenzene is
kinetically favored over side reactions when the molar
ratio of Lewis acid-to-aroyl halide is large, i.e.,
preferably at least about 1.5 : 1.

30 As used herein, the term "isomerically pure 2,5-
dichlorobenzophenones" means that, focusing on the
dichlorophenyl group of the final product, and as
determined by standard analytical methods, including
without limitation, gas chromatography (GC), high
35 pressure liquid chromatography (HPLC) and the like,
greater than about 99.5% of the dichlorobenzophenone
(or substituted analog thereof) obtained is the 2,5-

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1 dichloro isomer, as opposed to 2,3-, 2,4-, and other
possible isomers. Thus, Friedel-Crafts benzylation of
1,4-dichlorobenzene using benzoyl halide and about 1.5
5 mole of aluminum trichloride per mole of benzoyl halide
yields 2,5-dichlorobenzo-phenone rather than 2,4-
dichlorobenzophenone, 3,4-dichlorobenzophenone or (any)
other isomer(s). Typically, no detectable
isomerization of the 1,4-dichlorobenzene occurs during
the reaction. In contrast, undesirable isomerization
10 has been reported in the literature when nitrobenzene
was used as a solvent. Additionally, if the 1,4-
dichlorobenzene starting material is isomerically
impure, isomers other than 2,5-dichlorobenzophenone can
result.

15 It is believed that the molar ratio of
dichlorobenzene to aroyl halide is also an important
reaction parameter, with best results being achieved
when the ratio ranges from about 1.2 : 1 to about 8 :
1 or even larger. When the ratio is less than about
20 1.1:1, aroylation proceeds much more slowly and the
yield of dichlorobenzophenone is significantly lower.
When a large excess of 1,4-dichlorobenzene is used, the
excess acts as a solvent. Other solvents can be used,
but 1,4-dichlorobenzene is preferred, if a solvent is
25 used. Nitrobenzene should be avoided, because of its
toxicity, expense, and the occurrence of isomerization
reported to accompany its use.

 Preferably, the Lewis acid catalyst is selected
from the group consisting of aluminum bromide, aluminum
30 chloride, aluminum iodide, antimony pentachloride,
boron tribromide, boron trichloride, boron trifluoride,
boron triiodide, ferric bromide, ferric chloride,
gallium trichloride, niobium pentahalides, phosphorus
trifluoride, stannic chloride, stannous halides,
35 tantalum pentahalides, titanium tetrahalides, zinc
chloride, Nafion® (a polymeric fluorinated sulfonic
acid), other solid acids such as acidic clays, metal

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1 phosphates, metal phosphonates, and the like, and
mixtures thereof. Acid catalysts useful for Friedel-
Crafts aroylation have been reviewed by Olah in
5 *Friedel-Crafts and Related Reactions, Part I*, G.A.
Olah, Ed., Wiley, N.Y., 1963. Anhydrous aluminum
chloride is most preferred. Without being bound by
theory, it is believed that when at least a modicum of
aroyl halide is mixed with 1,4-dichlorobenzene,
10 isomerization of the 1,4-dichlorobenzene -- upon
introduction of a Lewis acid -- is suppressed.

The aroylation reaction is run at a temperature of
from about 0° to about 250°C, preferably from about 80°
to about 170°C. It is preferred to carry out the
reaction under anhydrous conditions.

15 Pressure, the order of addition of reagents, and
reaction time are not critical parameters. Most
reactions are complete in three to five hours and give
2,5-dichlorobenzophenones in good yield. The end point
of reaction can be monitored by thin layer
20 chromatography and other analytical methods.

Work-up of the reaction mixture is
straightforward. After the reaction is complete, it is
quenched with water. Distillation of any excess 1,4-
dichlorobenzene, followed by filtration and/or
25 extraction, and recrystallization, gives an
isomerically pure 2,5-dichlorobenzophenone in good to
excellent yield. No isomers other than 2,5-
dichlorobenzophenones have been detected, using
analytical methods such as gas chromatography (GC) and
30 high pressure liquid chromatography (HPLC).

As noted above, when the relative amount of Lewis
acid is large, rather than small, the yield of
reaction, product purity, and speed of reaction are all
increased. However, use of a large excess of Lewis
35 acid creates a greater quantity of by-products which
must be disposed of. In particular, aluminum chloride
yields HCl, Al₂O₃, and aluminum chlorohydrates,

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1 $[Al_2(OH)_5Cl]_x$ during work-up of the reaction mixture. In contrast, excess 1,4-dichlorobenzene is readily recoverable and reusable.

5 2,5-Dichlorobenzophenones can be used as starting materials for general, pharmaceutical and polymer synthesis. For example, the use of such compounds in the preparation of substituted para-polyphenylenes should proceed readily by metal-catalyzed aryl coupling of the 2,5-dichlorophenyl group of these compounds.

10 Polyphenylenes formed from these compounds will have pendant side groups comprising the carbonyl and the aryl or pyridyl group bonded thereto.

EXAMPLES

15 The invention is further described below in several non-limiting and exemplary embodiments. All parts and percentages are by weight. Reactants are commercially available or, at a minimum, readily prepared using synthetic organic chemistry techniques

20 known to those skilled in the art. The reactions described below can be scaled up without affecting product yield. Yields are reported as net ("isolated") yields and/or "absolute" yields, the latter being determined by gas chromatography. The difference

25 between absolute and isolated yield reflects inefficiencies in the work-up of the reaction product.

EXAMPLE 1: 2,5-Dichlorobenzophenone

30 To a 22 L, three-necked flask fitted with a thermometer, mechanical stirrer and a Vigreux column connected to an aqueous NaOH scrubbing tower, was added 1,4-dichlorobenzene (3 Kg, 26.4 mol) and benzoyl chloride (2.6 Kg, 18.55 mol). The mixture was heated to 80°C to give a homogeneous solution. Aluminum

35 chloride (5.5 Kg, 41.25 mol) was added over 12 min. with stirring. (The molar ratio of reactants was 2.2 : 1.4 : 1.0 ($AlCl_3$: Dichlorobenzene : Benzoyl

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1 Chloride)). The resulting mixture was heated to 140°C
over 60 min followed by heating to 175°C over 30 min.
Heating was stopped at 175°C. The mixture was allowed
to cool to 80°C over two hours and poured into a well
5 stirred mixture of ice and water (ca. 25 L water and 15
Kg of ice) over 30 min. The organic solid was
collected by filtration and dissolved in 7 L of
toluene. The solution was washed with aqueous sodium
bicarbonate and dried. Toluene was removed by
10 distillation. Pure 2,5-dichlorobenzophenone was
isolated in 80% yield after recrystallization from
hexane and toluene. Gas chromatography indicated an
absolute yield of 97%.

15 EXAMPLE 2: 2,5-Dichloro-2'-methylbenzophenone

A mixture of 22 ml (0.17 mol) of 2-toluoyl
chloride and 60 g (0.45 mol) of aluminum chloride in
120 g (0.82 mol) of 1,4-dichlorobenzene was heated at
170°C with stirring in a round-bottom flask fitted with
20 a condenser and a trap containing aqueous NaOH for
collecting effluent gases. (The molar ratio of
reactants was 2.6 : 4.8 : 1.0 (AlCl₃ : Dichlorobenzene
: 2-Toluoyl Chloride)). After the solution was heated
for 3.5 hours at this temperature, it was cooled to
25 about 100°C, poured into ice-water and extracted with
ether. The ethereal solution was distilled at
atmosphere to remove ether and then distilled at
reduced pressure to remove dichlorobenzene. The
residue was dissolved in hexane and decolorized with
30 charcoal. Evaporation of the solvent gave crude
product. Pure 2,5-dichloro-2'-methylbenzophenone
(11 g, 59% isolated yield) was obtained after the crude
product was recrystallized twice from hexane.

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1 EXAMPLE 3: 2,5-Dichloro-3'-methylbenzophenone

 The procedure of Example 2 was followed, using 22
ml (0.17 mol) of 3-toluoyl chloride and 60 g (0.45 mol)
of aluminum chloride in 120 g (0.82 mol) of
5 1,4-dichloro-benzene. (The molar ratio of reactants
was 2.6 : 4.8 : 1.0 (AlCl₃ : Dichlorobenzene : 3-Toluoyl
Chloride)). Pure 2,5-dichloro-3'-methyl-benzophenone
was isolated in 53% yield after the crude product was
recrystallized twice from hexane.

10

 The following qualitative examples of benzylation
of 1,4-dichlorobenzene illustrate the importance of
using a large Lewis acid-to-aroyl halide ratio.

15

EXAMPLE 4

 A mixture of 40g (0.27 mol) of 1,4-
dichlorobenzene, 45g (0.34 mol) of aluminum chloride
and 200ml (1.72 mol) of benzoyl chloride was heated at
150°C. (The molar ratio of reactants was 0.20 : 0.16
20 : 1.00 (AlCl₃ : Dichloro-benzene : Benzoyl Chloride)).
The color of the mixture turned brownish. Evolution of
hydrogen chloride gas was observed from the beginning
of the reaction. After 3 hours, gas evolution
virtually ceased, but heating was continued overnight
25 to ensure completion of reaction. A very deep color
was observed. Analysis by chromatography showed the
formation of a small amount of 2,5-dichlorobenzophenone
and large amounts of undetermined impurities.

30

EXAMPLE 5

 The reaction was carried out as in Example 4, but
with 7ml (0.06 mol) of warm 1,4-dichlorobenzene, 6g
(0.045 mol) of aluminum chloride and about 5ml (0.043
mol) of benzoyl chloride. (The molar ratio of
35 reactants was 1.05 : 1.40 : 1.00 (AlCl₃ :
Dichlorobenzene : Benzoyl Chloride)). After heating
the mixture as in Example 4, a deep color was observed.

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1 Chromatographic analysis of the reaction mixture
indicated that 2,5-dichlorobenzophenone had been
produced in only low yield, along with other
impurities. The conversion of benzoyl chloride
5 appeared slow.

EXAMPLE 6

A test tube was charged with 2ml of
1,4-dichlorobenzene and a few drops of benzoyl chloride
10 (50-100mg). About 500 mg of aluminum chloride (5-10
equivalents per equivalent of benzoyl chloride) was
added. The yellow suspension was heated with a heating
gun for about 2 minutes. (The temperature was about
200°C.) Part of the mixture was hydrolysed and
15 extracted with ether. Chromatography showed very pure
2,5-dichlorobenzophenone. Almost all of the benzoyl
chloride had been consumed.

EXAMPLES 7 THROUGH 10

20 In each of examples 7 through 10, the following
general procedure was followed, using the amount of
reactants indicated below in Table 1.

GENERAL PROCEDURE

25 A mixture of 1,4-dichlorobenzene and benzoyl
chloride was stirred at 80°C. Aluminum chloride was
added to the mixture in one portion and the resulting
mixture was stirred at 170°C for 7 hours. The crude
mixture was cooled to room temperature and hydrolysed
30 with water. The organic material was extracted into
ether and analyzed with thin layer chromatography and
gas chromatography, as described below.

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TABLE 1Starting Materials and Yields for Examples 7 Through 10

5	<u>Example</u>	Mass in grams	Millimoles	Molar ratio	<u>%Yield³</u>
		<u>(AlCl₃/DCB¹/BC²)</u>	<u>(AlCl₃/DCB/BC)</u>	<u>(AlCl₃/DCB/BC)</u>	
	7	2.1/6.17/2	15.8/42/14.2	1.1/3/1	73
	8	2.1/2.7/2	15.8/18.4/14.2	1.1/1.3/1	50
	9	2.42/6.17/2	18.2/42/14.2	1.1/3/1	85
	10	2.8/6.17/2	21/42/14.2	1.5/3/1	95

10

¹ DCB is 1,4-dichlorobenzene.² BC is benzoyl chloride.³ Yields are absolute yields of the 2,5-dichloro isomer of dichlorobenzophenone, as determined by gas chromatography, using 3-chlorobenzophenone as the internal standard. No other isomers were detected.

15

EXAMPLE 11

A mixture of 5.4 g of 1,4-dichlorobenzene, 4.2 g of aluminum chloride and 0.5 ml of benzoyl chloride was stirred at 170°C. Additional benzoyl chloride, up to a total of 4 g, was slowly added to the mixture over 2.5 hours, and the resulting mixture was stirred for another hour at 170°C. The molar ratio of reactants was 1.1/1.3/1 (AlCl₃ : Dichlorobenzene : Benzoyl Chloride). After work-up of the crude mixture as in Examples 7 through 10, 2,5-dichlorobenzophenone was obtained in 64% yield, as determined by gas chromatography using 3-chlorobenzophenone as the internal standard.

25

ANALYTICAL TECHNIQUES

30

In each of Examples 7 through 11, gas chromatography was performed with an HP-5830A gas chromatograph with the following parameters: column : 10% SP-2100 on 80/100 SUPELCOPORT; carrier gas: helium; detector: TCD; temp.1: 140° C; time1: 1 min.; temp.2: 350° C; heating rate: 25° C/min.; injection temp.: 300° C; TCD temp.: 325° C; flow rate: 30ml/min. The retention time of 2,5-dichlorobenzophenone was 9.5 min.

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1 High pressure liquid chromatography was performed
with a Waters 600E multisolvent delivery system
equipped with a Waters 490E programmable
5 multiwavelength detector, with the following
parameters: column: NOVA-PAK 60A C18, 4 μ m, 3.9x150 mm;
mobile phase: acetonitrile/water (1:1); column head
pressure: 1236 psi; flow rate: 0.75 ml/min. The
retention time of 2,5-dichlorobenzophenone was 19.02
min., which was different from those of other
10 dichlorobenzophene isomers.

Thin layer chromatography showed that the purity
of the crude (pre-work-up) 2,5-dichlorobenzophenone
from examples 9 and 10 was much better than that of
examples 7, 8 and 11, with example 10 being the best
15 and example 8 the worst. Examples 8 and 11 were run
with identical molar ratios for starting materials, but
absolute yields of 50 and 64%, respectively, were
obtained. Presumably, the difference in product yields
was due to the slower rate of addition of benzoyl
20 chloride to the reaction vessel in Example 11.

Comparison of the Present Invention with Past
Procedures

Table 2 compares the reaction parameters and
25 yields of 2,5-dichlorobenzophenone obtained in (A) the
earlier synthetic efforts of other investigators, and
(B) Examples 1 and 7 through 11 of the present
invention.

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Table 2

Comparison of Different Procedures of Friedel-Crafts
Benzoylation of 1,4-Dichlorobenzene

A. Prior Efforts

<u>Source</u>	<u>Molar ratio</u>		<u>Solvent</u>	<u>Temp.(°C)</u>	<u>Time</u>	<u>Yield(%)</u>
	<u>AlCl₃/DCB¹/BC²</u>					
Rec.Trav. Chim. Pay Bas 50, 767 (1931)	0.1/0.9/1		no	150-170	49 hr.	20
J. Prakt. Chem. 138, 311, (1933)	1.1/1.1/1		no	small flame	3 days	unspecified (low) ³
J. Chem. Soc. Chem. Commun. 856, (1967)	unspecified		no	150-170	49 hr.	16.5
Zh. Org. Khim. 1145, (1967); Tetrahedron 32, 843, (1976)	1.2/1.2/1		nitro- benzene	100	9.5 hr.	< 10
J. Chem. Soc. (C) 2452, (1968)	1/1.1/1		nitro- benzene	100	10 hr.	0.8

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B. Present Invention

<u>Example</u>	<u>AlCl₃/DCB/BC</u>	<u>Solvent</u>	<u>Temp. (°C)</u>	<u>Time</u>	<u>Yield⁴(%)</u>
1	2.2/1.4/1	no	80-175	≤3 hr.	97
5 7	1.1/3/1/	no	80-170	~7 hr.	73
8	1.1/1.3/1	no	80-170	~7 hr.	50
9	1.1/3/1	no	80-170	~7 hr.	85
10 10	1.5/3/1	no	80-170	~7 hr.	95
11	1.1/1.3/1	no	170	≥3.5 hr.	64

¹ DCB is 1,4-dichlorobenzene.

15 ² BC is benzoyl chloride.

³ A numerical value is not reported in the reference itself; however, a yield of 16.5% was reported by Pinkus and Meng (J. Chem. Soc. Chem. Commun. 856 (1967)) using the experimental method described in J. Prakt. Chem., 138, 311 (1933).

20 ⁴ Yields in examples 1 and 7 through 11 are absolute yields of the 2,5-dichloro isomer of dichlorobenzophenone, as determined by gas chromatography, using 3-chlorobenzophenone as the internal standard. As isolated yield of 80% was obtained in example 1.

25 As shown in Table 2, prior efforts to prepare 2,5-dichlorobenzophenone by Friedel-Crafts benzoylation of 1,4-dichlorobenzene have failed, typically resulting in the production of isomerically impure 2,5-dichlorobenzophenone in only poor yield. In contrast, Friedel-Crafts aroylation of 1,4-dichlorobenzene in accordance with the present invention is an inexpensive and straightforward method for preparing isomerically pure 2,5-dichlorobenzophenone in good to excellent yield.

30 The invention has been described in preferred and exemplary embodiments but is not limited thereto. Those skilled in the art will appreciate that various modifications can be made without departing from the scope of the invention, which is defined by the 35 following claims.

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1 WHAT IS CLAIMED IS:

1. A method for preparing 2,5-dichlorobenzo-phenones, comprising:

5 Friedel-Crafts aroylation of 1,4-dichlorobenzene using an aroyl halide or an aromatic anhydride, and at least one Lewis acid present in an amount of at least about 1.5 mole per mole of aroyl halide or aromatic anhydride.

10

2. A method according to claim 1, wherein said at least one Lewis acid is present in an amount of from about 2 to about 2.5 mole per mole of aroyl halide or aromatic anhydride.

15

3. A method according to claim 1 wherein the Lewis acid is selected from the group consisting of aluminum bromide, aluminum chloride, boron trichloride, boron trifluoride, ferric bromide, ferric chloride, stannic chloride, zinc chloride and mixtures thereof.

20

4. A method according to claim 1 wherein the Lewis acid is aluminum chloride.

25 5. A method according to claim 1, wherein the aroyl halide comprises a benzoyl halide having from 0 to 5 non-hydrogen substituents, or a heteoaroyl halide having from 0 to 4 non-hydrogen substituents, each of which said substituents does not interfere with aroylation and is bound to the aroyl halide directly or
30 through a carbon atom or a heteroatom selected from the group consisting of sulfur, phosphorus, oxygen, nitrogen and silicon.

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1 6. A method according to claim 1 wherein the
aroyl halide is selected from the group consisting of
benzoyl chloride, 1-naphthoyl chloride, 2-naphthoyl
chloride, 4-quinolinoyl chloride, nicotinoyl chloride,
5 isonicotinoyl chloride, p-toluoyl chloride, m-toluoyl
chloride, o-toluoyl chloride, phthaloyl chloride,
isophthaloyl chloride, terephthaloyl chloride,
4,4'-biphenyldicarbonyl chloride, 2,3-dimethylbenzoyl
chloride, 2,4-dimethylbenzoyl chloride,
10 2,5-dimethylbenzoyl chloride, 2,6-dimethylbenzoyl
chloride, 3,4-dimethylbenzoyl chloride,
3,5-dimethylbenzoyl chloride, 2-benzoylbenzoyl
chloride, 3-benzoylbenzoyl chloride, 4-benzoylbenzoyl
chloride, 2-fluorobenzoyl chloride, 3-fluorobenzoyl
15 chloride, 4-fluorobenzoyl chloride, 2-chlorobenzoyl
chloride, 3-chlorobenzoyl chloride, 4-chlorobenzoyl
chloride, 2-trifluoromethylbenzoyl chloride,
3-trifluoromethylbenzoyl chloride,
4-trifluoromethylbenzoyl chloride, 2-methoxybenzoyl
20 chloride, 3-methoxybenzoyl chloride, 4-methoxybenzoyl
chloride, 2-methoxycarbonylbenzoyl chloride, 3-methoxy-
carbonylbenzoyl chloride, 4-methoxycarbonylbenzoyl
chloride, 2-cyanobenzoyl chloride, 3-cyanobenzoyl
chloride, and 4-cyanobenzoyl chloride.

25
7. A method according to claim 1, wherein the
aromatic anhydride is selected from the group
consisting of phthalic anhydride, substituted phthalic
anhydrides, benzoic anhydride, and substituted benzoic
30 anhydrides.

8. A method according to claim 1, wherein
1,4-dichlorobenzene and the aroyl halide are present in
a ratio of at least about 1.2 mole of
35 1,4-dichlorobenzene per mole of the aroyl halide.

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1 9. A method according to claim 8 wherein the
ratio of 1,4-dichlorobenzene to aroyl halide ranges
from about 1.2 : 1 to about 8 : 1.

5 10. A method according to claim 1 wherein the
Friedel-Crafts aroylation is carried out at a
temperature of from about 0 to about 250°C.

10 11. A method according to claim 10 wherein the
Friedel-Crafts aroylation is carried out at a
temperature of from about 80 to about 170°C.

15 12. A method according to claim 1, wherein the
2,5-dichlorobenzophenones are isomerically pure.

20 13. A method for preparing 2,5-
dichlorobenzophenones, comprising: Friedel-Crafts
aroylation of 1,4-dichlorobenzene using an aroyl halide
or an aromatic anhydride, and at least one Lewis acid,
in the absence of nitrobenzene; wherein the molar ratio
of Lewis acid to 1,4-dichlorobenzene to aroyl halide or
aromatic anhydride is no less than about 1.1 : 1.3 : 1,
and the 2,5-dichlorobenzophenones are obtained in at
least about 50% yield.

25 14. A method according to claim 13, wherein the
Lewis acid is present in an amount of from about 2 to
about 2.5 mole per mole of aroyl halide or aromatic
anhydride.

30 15. A method according to claim 12, wherein the
Lewis acid is selected from the group consisting of
aluminum bromide, aluminum chloride, boron trichloride,
boron trifluoride, ferric bromide, ferric chloride,
35 stannic chloride, zinc chloride and mixtures thereof.

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1 16. A method according to claim 13, wherein the
Lewis acid is aluminum chloride.

5 17. A method according to claim 13, wherein the
aroyl halide is selected from the group consisting of
benzoyl chloride, 1-naphthoyl chloride, 2-naphthoyl
chloride, 4-quinolinoyl chloride, nicotinoyl chloride,
isonicotinoyl chloride, p-toluoyl chloride, m-toluoyl
10 chloride, o-toluoyl chloride, phthaloyl chloride,
isophthaloyl chloride, terephthaloyl chloride,
4,4'-biphenyldicarbonyl chloride, 2,3-dimethylbenzoyl
chloride, 2,4-dimethylbenzoyl chloride,
2,5-dimethylbenzoyl chloride, 2,6-dimethylbenzoyl
chloride, 3,4-dimethylbenzoyl chloride,
15 3,5-dimethylbenzoyl chloride, 2-benzoylbenzoyl
chloride, 3-benzoylbenzoyl chloride, 4-benzoylbenzoyl
chloride, 2-fluorobenzoyl chloride, 3-fluorobenzoyl
chloride, 4-fluorobenzoyl chloride, 2-chlorobenzoyl
chloride, 3-chlorobenzoyl chloride, 4-chlorobenzoyl
20 chloride, 2-trifluoromethylbenzoyl chloride,
3-trifluoro-methylbenzoyl chloride,
4-trifluoromethylbenzoyl chloride, 2-methoxybenzoyl
chloride, 3-methoxybenzoyl chloride, 4-methoxybenzoyl
chloride, 2-methoxycarbonylbenzoyl chloride, 3-methoxy-
25 carbonylbenzoyl chloride, 4-methoxycarbonylbenzoyl
chloride, 2-cyanobenzoyl chloride, 3-cyanobenzoyl
chloride, and 4-cyanobenzoyl chloride.

30 18. A method according to claim 13, wherein the
aromatic anhydride is selected from the group
consisting of phthalic anhydride, substituted phthalic
anhydrides, benzoic anhydride, and substituted benzoic
anhydrides.

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1 19. A method according to claim 13, wherein
1,4-dichlorobenzene and the aroyl halide are present in
a ratio of at least about 1.2 mole of
1,4-dichlorobenzene per mole of aroyl halide.

5 20. A method according to claim 19, wherein the
ratio of 1,4-dichlorobenzene to aroyl halide ranges
from about 1.2 : 1 to about 8 : 1.

10 21. A method according to claim 13, wherein
aroylation is carried out at a temperature of from
about 0 to about 250°C.

15 22. A method according to claim 20, wherein
aroylation is carried out at a temperature of from
about 80 to about 170°C.

20 23. A method for preparing 2,5-dichlorobenzo-
phenones, comprising:
heating a mixture of 1,4-dichlorobenzene, an
aroyl halide or an aromatic anhydride, and at least one
Lewis acid present in an amount of at least about 1.5
mole per mole of aroyl halide or aromatic anhydride.

25 24. A method according to claim 23, wherein said
at least one Lewis acid is present in an amount of from
about 2 to about 2.5 mole per mole of aroyl halide or
aromatic anhydride.

30 25. A method according to claim 23 wherein the
Lewis acid is selected from the group consisting of
aluminum bromide, aluminum chloride, boron trichloride,
boron trifluoride, ferric bromide, ferric chloride,
stannic chloride, zinc chloride and mixtures thereof.

35 26. A method according to claim 23 wherein the
Lewis acid is aluminum chloride.

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1 27. A method according to claim 23, wherein the
 aroyl halide comprises a benzoyl halide having from 0
 to 5 non-hydrogen substituents, or a heteroaroyl halide
 having from 0 to 4 non-hydrogen substituents, each of
5 which said substituents does not interfere with
 aroylation and is bound to the aroyl halide directly or
 through a carbon atom or a heteroatom selected from the
 group consisting of sulfur, phosphorus, oxygen,
 nitrogen and silicon.

10 28. A method according to claim 23 wherein the
 aroyl halide is selected from the group consisting of
 benzoyl chloride, 1-naphthoyl chloride, 2-naphthoyl
 chloride, 2-quinolinoyl chloride, nicotinoyl chloride,
15 isonicotinoyl chloride, p-toluoyl chloride, m-toluoyl
 chloride, o-toluoyl chloride, phthaloyl chloride,
 isophthaloyl chloride, terephthaloyl chloride,
 4,4'-biphenyldicarbonyl chloride, 2,3-dimethylbenzoyl
 chloride, 2,4-dimethylbenzoyl chloride,
20 2,5-dimethylbenzoyl chloride, 2,6-dimethylbenzoyl
 chloride, 3,4-dimethylbenzoyl chloride,
 3,5-dimethylbenzoyl chloride, 2-benzoylbenzoyl
 chloride, 3-benzoylbenzoyl chloride, 4-benzoylbenzoyl
 chloride, 2-fluorobenzoyl chloride, 3-fluorobenzoyl
25 chloride, 4-fluorobenzoyl chloride, 2-chlorobenzoyl
 chloride, 3-chlorobenzoyl chloride, 4-chlorobenzoyl
 chloride, 2-trifluoromethylbenzoyl chloride,
 3-trifluoro-methylbenzoyl chloride,
 4-trifluoromethylbenzoyl chloride, 2-methoxybenzoyl
30 chloride, 3-methoxybenzoyl chloride, 4-methoxybenzoyl
 chloride, 2-methoxycarbonylbenzoyl chloride, 3-methoxy-
 carbonylbenzoyl chloride, 4-methoxycarbonylbenzoyl
 chloride, 2-cyanobenzoyl chloride, 3-cyanobenzoyl
 chloride, and 4-cyanobenzoyl chloride.

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1 29. A method according to claim 23 wherein the
aromatic anhydride is selected from the group
consisting of phthalic anhydride, substituted phthalic
anhydrides, benzoic anhydride, and substituted benzoic
5 anhydrides.

 30. A method according to claim 23, wherein
1,4-dichlorobenzene and the aroyl halide are present in
a ratio of at least about 1.2 mole of
10 1,4-dichlorobenzene per mole of aroyl halide.

 31. A method according to claim 30 wherein the
ratio of 1,4-dichlorobenzene to aroyl halide ranges
from about 1.2 : 1 to about 8 : 1.
15

 32. A method according to claim 23 wherein the
mixture is heated at a temperature of from about 0 to
about 250°C.

20 33. A method according to claim 32, wherein the
mixture is heated at a temperature of from about 80 to
about 170°C.

 34. A method according to claim 23, wherein the
25 2,5-dichlorobenzophenones are isomerically pure.

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INTERNATIONAL SEARCH REPORT

PCT/US92/10422

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :C07C 45/45

US CL :568/319,322,323

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 568/319,322,323

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A, 3,395,115 (Milionis et al.) 30 July 1968 See the entire document.	1-34
X	US,A, 4,094,992 (Kaplan et al.) 13 June 1978 See the entire document.	1-34
X	US,A, 4,530,844 (Smerbeck et al.) 23 July 1985 See the entire document.	1-34
X	US,A, 4,960,945 (Terauchi et al.) 02 October 1990 See the entire document.	1-34
X	GB,A, 1,135,358 (Helden et al.) 04 December 1968 See the entire document.	1-34

☒ Further documents are listed in the continuation of Box C: ☐ See patent family annex.

* Special categories of cited documents:	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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Date of the actual completion of the international search

19 JANUARY 1993

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/10422

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB,A, 1,118,864 (Schulze-Steinen et al.) 05 April 1966 See the entire document.	1-34